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Correlation of fatigue with other disease related and psychosocial factors in patients with rheumatoid arthritis treated with tocilizumab
ACT-AXIS study

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Abstract

To assess the hypothesis if tocilizumab (TCZ) is effective on disease activity, and also its effect in fatigue and other clinical and psychological disease-related factors in patients with rheumatoid arthritis (RA) treated with TCZ.

A 24-week, multicenter, prospective, observational study in patients with moderate to severe RA receiving TCZ after failure or intolerance to disease-modifying antirheumatic drugs or tumor necrosis factor-alpha was conducted.

Of the 122 patients included, 85 were evaluable for effectiveness (85% female, 51.9 ± 12.5 years, disease duration 8.7 ± 7.4 years). Mean change in C-reactive protein level from baseline to week 12 was -11.2 ± 4.0 ($P < .001$). Mean Disease Activity Index score (DAS28) decreased from 5.5 ± 1.0 at baseline to 2.7 ± 1.3 ($P < .001$) at week 24. Mean change in Functional Assessment of Chronic Illness Therapy score was -5.4 ± 11.2 points at week 24. Multiple regression analysis showed that the improvement in DAS28, sleep, and depression explained 56% and 47% of fatigue variance at week 12 and 24, respectively.

Tocilizumab is effective in reducing disease activity and results in a clinically significant improvement in fatigue, pain, swollen joint count, morning stiffness, sleepiness, depression, and DAS28; the last 3 were specifically identified as factors explaining fatigue variance with the use of TCZ in RA patients.

Abbreviations: AEs = adverse events, BDI-II = Beck Depression Inventory, version II, CRP = C-reactive protein, DAS28 = Disease Activity Index score, DMARDs = disease-modifying antirheumatic drugs, ESR = erythrocyte sedimentation rate, EULAR = European League Against Rheumatism, FACIT-F = Functional Assessment Chronic Illness Therapy-Fatigue scale, HPA = hypothalamic-pituitary-adrenal, IL = interleukin, PROs = patient-reported outcomes, RA = rheumatoid arthritis, SJC = swollen joint count, TCZ = tocilizumab, TJC = tender joint count, SAEs = serious adverse events, TNF-alfa = tumor necrosis factor-alpha, VAS = visual analog scale.

Keywords: clinical practice, fatigue, patient-reported outcomes, rheumatoid arthritis, tocilizumab

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1. Introduction

The clinical picture of rheumatoid arthritis (RA) includes the joint and systemic involvement, and also several psychological aspects may be affected. Importantly, fatigue is 1 of the most common and disabling symptoms of RA. Although it is considered to contribute to a decline in the patient's health status and quality of life, fatigue rarely constitutes a treatment target in RA.[1] Fatigue has not been considered among the recommended criteria for RA management, despite being a reliable and sensitive measure of change in RA.[2]

The mechanisms for fatigue in RA are not entirely clear, as most of current evidence is derived from cross-sectional studies that do not allow identifying long-term predictors and potential causal pathways for RA fatigue. Disease activity and other disease-related factors such as excessive inflammation have been reported to be correlated with fatigue.[3] However, the relationship of fatigue to disease activity seems to be less strong than previously assumed,[4–6] or this association has been found to be secondary or indirectly mediated through pain.[4]

Discrepant findings have also been reported among those studies evaluating pain as a possible cause of fatigue, whose results vary from nonexistent[7,8] to a strong correlation based on cross-sectional and longitudinal studies.[9] The inflammatory process as a factor influencing RA fatigue has not been fully established, as weak associations between fatigue and erythrocyte sedimentation rate (ESR), tender and swollen joints, and Disease Activity Index score (DAS28), or even absent for rheumatoid factor, ESR, and hemoglobin levels, have been described.[10–12]

Psychological factors seem to play a crucial role in explaining fatigue.[4,6,8,12] The contribution of disease activity to fatigue has been explained by mechanisms of mood and sleep disorders.[13] These findings support the widely accepted model of multifactorial etiology for fatigue, which has recently incorporated personal life aspects as factors that may be inter or intrarelated with other RA disease factors, and behavioral/cognitive issues.[14]

Tocilizumab (TCZ) has demonstrated drug efficacy and a safety profile in RA for more than 8 years to date. Considering the complexity of fatigue in RA, it is difficult to obtain conclusive data regarding the effect of treatment on this symptom.[15] Relief of fatigue in RA patients receiving interleukin (IL)-6 blocking agents,[16,17] suggests a biological pathway target for these agents through the hypothalamic-pituitary-adrenal (HPA) axis, given its activation by IL-6.[18,19] The fact that disturbance of the HPA axis may also influence other RA symptoms[18] led us to the hypothesis that a possible change in fatigue with the anti-IL-6 receptor antibody TCZ may be explained not only through its effect on disease activity but also on other RA-related, and physical and psychosocial factors.

The aim of the ACT-AXIS study was to assess efficacy of TCZ on disease activity and to identify factors associated with fatigue, and other clinical and psychological disease-related factors in patients with RA treated with TCZ after failure or intolerance to disease-modifying antirheumatic drugs (DMARDs) or tumor necrosis factor (TNF)-inhibitors.

2. Methods

2.1. Study design

The ACT-AXIS study was a multicenter, prospective observational study conducted in rheumatology units of 15 Spanish hospitals. The study was conducted in accordance with the Declaration of Helsinki and national regulations. The study was approved by the Ethic Committee of the Hospital de Sant Joan Despí Moisès Broggi, Barcelona (Spain), and all patients gave their written informed consent. Patients were followed up for 24 weeks according to clinical practice.

2.2. Study population

Inclusion criteria: adult (age ≥18 years) patients with moderate to severe RA (fulfilling the American College of Rheumatology 1987 revised criteria for RA), nonresponders or intolerant to DMARDs or TNF-inhibitors, and for whom the rheumatologist had decided to initiate TCZ treatment according to routine clinical practice. Exclusion criteria: previous diagnostic of depression or other psychiatric condition, and exclusion of other inflammatory or autoimmune diseases. Administration of TCZ as clinical trial medication or compassionate therapy, an absolute neutrophil count $\leq 2 \times 10^9$/L in the last routine blood test available, and inability to complete the study questionnaires were the exclusion criteria.

2.3. Data collection and assessments

Baseline evaluation at the time of TCZ initiation included a complete medical history along with the following data that were also collected at baseline and at 2 routine follow-up visits closest to weeks 12 and 24: laboratory parameters (hemoglobin, hematocrit, C-reactive protein [CRP] and ESR), RA activity-related data (tender joint count [TJC], swollen joint count [SJC], DAS28 score, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's pain assessment, morning stiffness duration, fatigue, sleepiness, and depression), and personal and social aspects of life (marital status, children living at home, care for dependents employment status, significant events in life, duration of sleep [hours of sleep at night], and physical activity). Moreover, TCZ treatment-related data and adverse events were retrieved at routine monthly visits coinciding with TCZ administration.

The DAS28 was calculated for disease activity using the ESR,[20] and it ranges from 0 to 10, where a score above 5.1 indicates high disease activity, a score 3.2 to 5.1 represents moderate disease activity, and below 3.2 indicates low disease activity. Response to TCZ treatment was evaluated by the European League Against Rheumatism (EULAR) response criteria.[21] Patient's and physician's global assessment of disease activity and pain were evaluated using a 10-cm visual analog scale (VAS). Fatigue was assessed according to the Functional Assessment Chronic Illness Therapy-Fatigue scale (FACIT-F, version 4)[22]; a brief 13-item score ranged from 0 to 52, where a high score represents less fatigue and a 3 to 4-point change is considered clinically significant. Depression was measured using the Beck Depression Inventory, version II (BDI-II),[23,24] which contains 21 questions scored on a scale value of 0 (neutral) to 3 (maximal severity). Total scores range from 0 to 63, and a higher total score corresponds to more severe depressive symptoms. A total score over 18 indicates moderate to severe depression. Sleepiness was evaluated by the Epworth Sleepiness Scale,[25] which is intended to evaluate the probability of falling asleep in 8 situations reflecting activities of daily living in a score from 0 "never doze or sleep" to 3 "high chance of dozing or sleeping." Total score ranges from 0 to 24, where the higher the score, the higher the sleepiness level.

2.4. Statistical analysis

The primary endpoint was to evaluate the correlation between change in fatigue and disease-related factors (serum hemoglobin levels, SJC, morning stiffness, pain, sleepiness, and depression) with the use of TCZ. We also seek for the influence of personal aspects (marital status, children living at home, care for dependents, employment status, important events in life, physical activity, time in hours of sleep at night) on the changes described. A simple linear regression model was used to calculate the individual correlation. The change in fatigue (from baseline to weeks 12 and 24) as the dependent variable was regressed against the change in each of the abovementioned disease-related variables, and personal and social aspects to assess the individual correlation. All variables that had a significance level of $P \leq .10$ were subsequently included in a multivariate linear regression analysis using an automatic stepwise selection model to identify the factors explaining fatigue variance. The β-regression coefficient, beta standardized regression coefficient, and the coefficient of determination (R^2) were calculated, the latter to determine the variance of change in fatigue explained by the independent variables included in the model.

Secondary endpoints included changes from baseline to week 12 and 24 for hemoglobin and CRP levels, SJC, pain score, morning stiffness duration, fatigue, sleepiness, and depression scores. We also evaluated the potential correlation between fatigue and anemia, defined as hemoglobin levels <12 g/dL in women and <13 g/dL in men. CRP, SJC, and DAS28 values were used to assess disease activity and response to the treatment. Clinical efficacy was assessed by a decrease in DAS28 score from baseline to weeks 12 and 24, and EULAR responses. Remission was defined, in accordance with the EULAR definition, as DAS28 <2.6. Safety was assessed by the frequency, severity, and causality of adverse events (AEs) reported during the study period.

Only patients with FACIT questionnaires scores available at baseline and 12 and 24 weeks after treatment initiation were considered evaluable for the effectiveness analysis.

Descriptive analysis was used for secondary endpoints, with continuous variables expressed as either mean ± standard deviation (SD) or as median (interquartile range) according to their distribution, and categorical variables as percentage. The change in each variable from baseline to week 12 and 24 was calculated by paired-samples t test (parametric) or Wilcoxon signed-rank tests (nonparametric).

The statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Patient characteristics

Between September, 2012 and May, 2015, a total of 122 patients were enrolled in the study. Two patients were excluded from the study since they did not meet selection criteria. Thirty-five patients were excluded from the effectiveness analysis due to the lack of FACIT questionnaire scores at any of the study visits. Therefore, the evaluable population for the effectiveness analysis comprised a total of 85 patients. Premature withdrawal from the study occurred in 4 patients. The patient flowchart is shown in Fig. 1. Patient demographic and clinical baseline characteristics are described in Table 1.

3.2. Tocilizumab treatment

Most patients received TCZ at a dose of 8 mg/kg. Ten (11.8%) patients required treatment dose adjustments due to laboratory abnormalities (n=4), weight gain (n=7), adverse events (n=1), and other unspecified reasons (n=3). Of these, 8 patients required 1 or 2 dose modifications. Six (7.1%) patients required at least 1 temporary interruption of TCZ, mainly due to adverse events (n=4). During the 24-week period, 4 (4.7%) patients discontinued TCZ due to insufficient response (n=3) and adverse events (n=1). The majority of patients received TCZ combined with MTX for RA (91.8%), and at that time point of the analysis, 68 patients were receiving low doses of prednisone (<5 m/daily).

3.3. Clinical efficacy of tocilizumab

The SJC and CRP levels were significantly reduced after 12 weeks of TCZ treatment (mean change from baseline of −4.0±4.7 [$P<.001$] and −11.2±4.0 [$P<.001$], respectively). By week 24, mean baseline DAS28 had decreased 2.7±1.4 points ($P<.001$) (Table 2). In addition, after 24 weeks of TCZ initiation, EULAR responses were good in 44 (62.0%) patients, moderate in 22 (31.0%) patients, and absent in 5 (7%). The proportion of patients who experienced disease remission within 24 weeks was 45.2% (Fig. 2).

3.4. Effect of tocilizumab on fatigue and RA-related factors in active RA

After 24 weeks of TCZ, there was a clinically significant mean change in FACIT-F score of 5.4±11.2 points from baseline ($P<.001$) (Table 2). Patients with significant fatigue (FACIT-F score <30) decreased from 58.8% at baseline to 37.6% by week 24.

Hemoglobin levels significantly increased in 0.6±1.1 points by week 24 ($P<.001$). Accordingly, patients with anemia decreased from 65.9% at baseline to 47.9% at week 24. Mean scores for pain and depression, and mean duration of morning stiffness were significantly reduced by week 12, with a mean change that was sustained at week 24 (Table 2).

3.5. RA-related factors that may contribute to fatigue in RA

Simple linear regression analysis showed that change on FACIT-F score seen was significantly correlated with change in DAS28e ($\beta=-3.241$, $P<.01$), pain ($\beta=-0.947$, $P=.037$), sleepiness ($\beta=-0.742$, $P=.003$), and depression ($\beta=-0.714$, $P<.001$) at week 12.

When the association with change in FACIT-F score at week 24 was analyzed, significant correlations were observed with the change in DAS28 ($\beta=-2.596$, $P<.01$), SJC ($\beta=-0.600$, $P=.022$), pain ($\beta=-0.838$, $P=.044$), sleepiness ($\beta=-1.193$, $P=.001$), and depression scores ($\beta=-0.777$, $P<.001$).

Fatigue outcome was associated neither with hemoglobin levels and morning stiffness duration, nor with any of the personal life aspects.

Multiple linear regression analysis showed that the independent change in DAS28, sleepiness depression scores explained 56% and 47% of fatigue variance at weeks 12 and 24, respectively (Table 3).
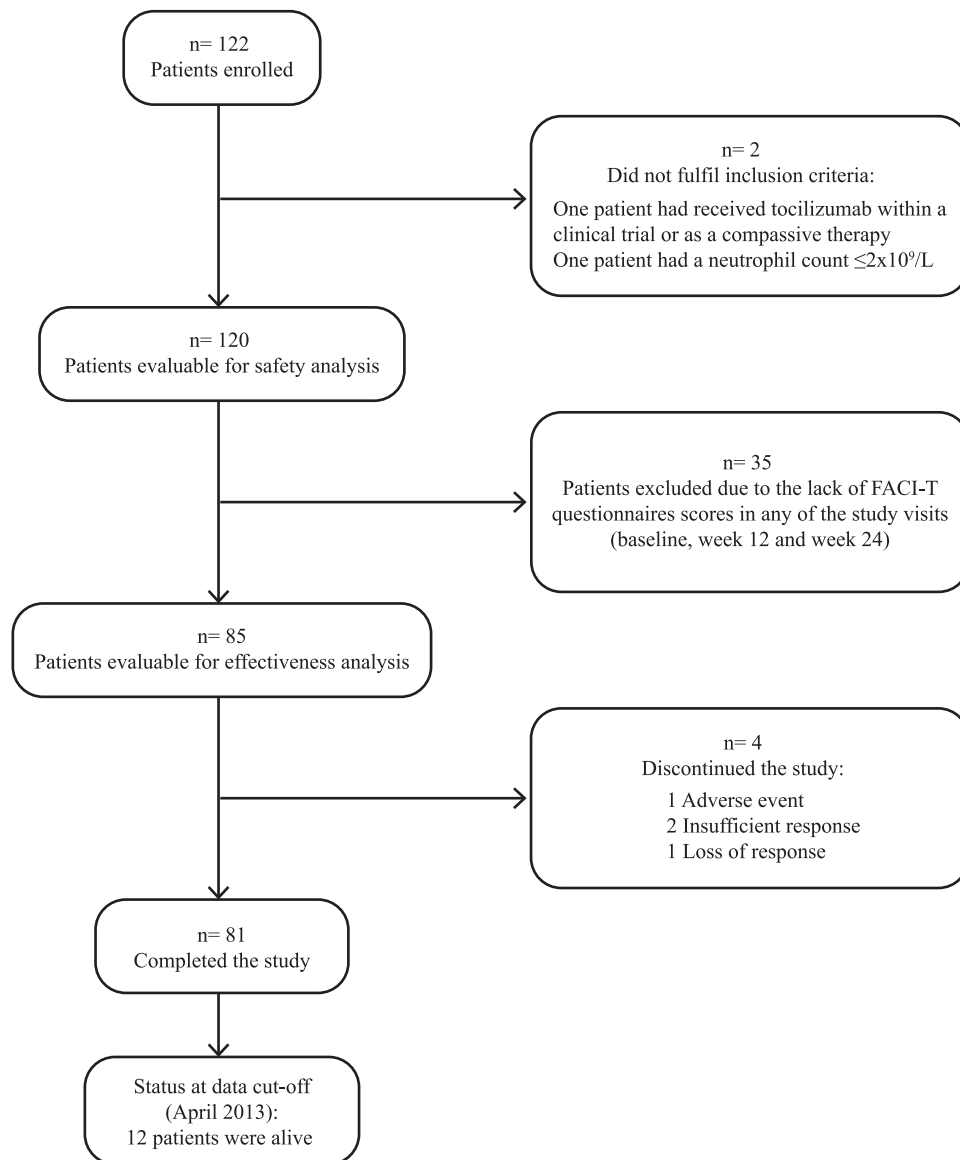
Figure 1. Disposition of patients. Flowchart diagram of the number of patients included in the study.

3.6. Safety

In all, 120 patients were included in the safety analysis. Overall, 195 AEs were reported in 77 (64.2%) patients. Most adverse events were mild (76.9%) to moderate (20.5%), and 48 AEs were considered as related to TCZ in 28 (23.3%) patients. Hypercholesterolemia and hypertransaminasemia were the most common adverse reactions in 11 (9.2%) and 4 (3.3%) patients, respectively. Only 3 patients experienced treatment-related infections. Infusion-related adverse reactions occurred in 7 (5.8%) patients. Seven (3.6%) serious AEs (SAEs) were reported in 6 patients: infectious arthritis, pilonidal cyst, acute endocarditis, acute pyelonephritis, respiratory tract infection, respiratory failure, and rheumatoid lung disease.

4. Discussion

To our knowledge, this is the first study focusing on the correlation of fatigue with other disease-related and psychosocial factors in patients with RA treated with TCZ in routine clinical practice. Our findings show that TCZ results in a clinically significant improvement in fatigue in patients with moderate to severe RA. Fatigue outcome was significantly correlated with improvement in SJC, DAS28, pain, sleepiness, and depression after TCZ treatment, although only depression, sleepiness, and DAS28 seemed to explain fatigue variance.

The efficacy data show that TCZ is effective in reducing disease activity,[26–28] as reflected by the significant decrease in DAS28, in line with clinical trials with this targeted treatment.[26–28] In addition, high remission levels were achieved by week 12 that were maintained and even slightly increased after 24 weeks from treatment initiation. The notable decrease in SJC and CRP levels also revealed a significant improvement in initial inflammatory activity. The high remission rates observed are those expected considering the beneficial effect of TCZ on acute-phase reactants.[29] In addition, we found that hemoglobin levels increased significantly after TCZ therapy as previously seen.[30]

Table 1

Baseline demographics, clinical characteristics, and PROs (n=85).

Characteristics	Value
Age, y (mean±SD)	51.9±12.5
Female; n (%)	72 (84.7)
Duration of RA, y (mean±SD)	8.7±7.4
ESR, mm/h (mean±SD)*	44.8±26.3
CRP, mg/dL (mean±SD)†	13.0±19.0
Hemoglobin, g/dL (mean±SD)	12.5±1.5
Tender joint count (mean±SD)	8.8±6.9
Swollen joint count (mean±SD)	6.0±4.6
DAS28 (mean±SD)‡	5.5±1.0
Tociluzumab in combination with MTX	91.8 (%)
Patient's global assessment (VAS), cm (mean±SD)	6.8±2.1
Physician's global assessment (VAS), cm (mean±SD)	6.0±2.1
Pain VAS, cm (mean±SD)	6.6±2.3
Morning stiffness, h (mean±SD)	1.4±2.7
FACIT-F fatigue score (mean±SD)	26.8±12.4
Epworth sleepiness score (mean±SD)	6.0±4.6
Beck Depression Score (mean±SD)	17.2±11.8

CRP = C-reactive protein, DAS28 = Disease Activity Index score, ESR = erythrocyte sedimentation rate, FACIT-F = Functional Assessment Chronic Illness Therapy-Fatigue scale, PROs = patient-reported outcomes, RA = rheumatoid arthritis, SD = standard deviation, VAS = visual analog scale.
* Missing data (n=4).
† Missing data (n=10).
‡ Missing data (n=4).

Table 2

Mean changes in fatigue and RA disease factors from baseline to 12 and 24 weeks.

Variable	Week 12	P*	Week 24	P*
Fatigue (FACIT-F score)	4.6±10.5	<.001	5.4±11.2	<.001
Hemoglobin levels (g/dL)	0.7±1.0	<.001	0.6±1.1	<.001
CRP (mg/L)	−11.2±4.0	<.001	−12.5±21.3	<.001
SJC	−4.0±4.7	<.001	−4.2±4.7	<.001
DAS28	−2.5±1.2	<.001	−2.7±1.4	<.001
Morning stiffness (h)	−0.9±2.9	<.001	−1.0±2.7	<.001
Pain VAS (cm)	−2.6±2.5	<.001	−2.6±3.0	<.001
Epworth sleepiness score	−0.4±4.5	.172	−0.8±3.4	<.05
Beck Depression Score	−3.1±9.1	<.001	−3.5±9.0	<.005

CRP = C-reactive protein, FACIT = Functional Assessment Chronic Illness Therapy-Fatigue scale, SJC = swollen joint count, VAS = visual analog scale.
* Based on paired-samples t test.

The increase in hemoglobin levels could be reflecting declines in hepcidin after TCZ, which previous research has associated with an improvement of inflammatory anemia together with CRP reductions.[31] Our findings therefore support the beneficial effect of TCZ in decreasing inflammatory activity and improving functioning in patients with active RA under routine clinical practice conditions.

Consistent with previous efficacy reports,[27,32] we found that TCZ treatment resulted in a clinically significant improvement in fatigue (≥4 points in FACIT-F)[33] that was even enhanced over

time. Accordingly, the high proportion of RA patients with significant fatigue decreased approximately 20% by week 24. Patient-reported outcomes (PROs) on pain, morning stiffness, and depression were notably improved by week 12, and the beneficial effect was sustained over time. Despite the association of disease activity with morning stiffness,[34] pain, and depression,[35,36] we cannot conclude that the improved PROs are derived from the reduction in disease activity after TCZ treatment. Morning stiffness and pain have been linked to high levels of IL-6 during early morning in patients with active RA.[37,38] Additionally, depression in RA has been reported to be mediated by the up-regulation of cytokines known to be associated to the HPA axis.[39] The potential effect of TCZ to inhibit IL-6 may therefore contribute to its efficacy in reducing these symptoms, providing both clinical and psychosocial benefit in significantly fatigued patients.

Our findings show that fatigue outcome was significantly correlated with improvement in disease activity measured by DAS28 and SJC, and also with pain, sleepiness, and depression after TCZ treatment, although only DAS28, sleepiness, and
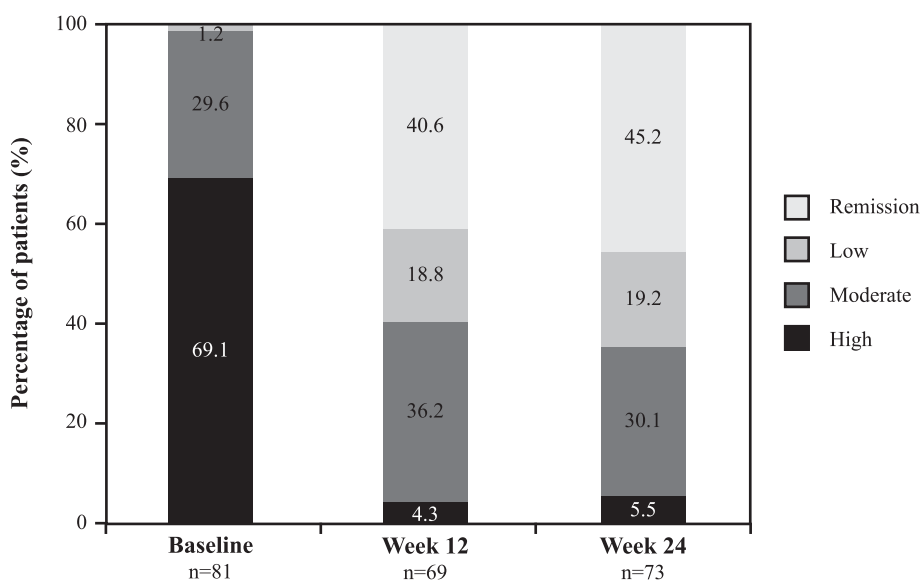
Figure 2. Disease activity over time. Disease activity was assessed according to DAS28 score. Percentage of patients achieving remission, low, moderate and high disease activity according to EULAR criteria are exposed: remission: DAS28 <2.6, low disease activity: 2.6 <DAS28 ≤ 3.2, moderate disease activity: 3.2 < DAS28 ≤ 5.1, high disease activity: DAS28 >5.1. DAS28 = Disease Activity Index score, EULAR = European League Against Rheumatism.

Table 3

Factors associated with fatigue in RA by multiple regression analysis.

Variable	β-coefficient[*]	Beta[†]	95% CI	P
Change from baseline to week 12[‡]				
DAS28 score	−2.200	−0.251	−3.741 to −0.658	<.01
Epworth sleepiness score	−0.944	−0.381	−1.371 to −0.518	<.001
Beck depression score	−0.707	−0.590	−0.919 to −0.494	<.001
Constant term	−2.822			
$R^2 = 0.558$				
Change from baseline to week 24[§]				
DAS28 score	−1.743	−0.215	−3.242 to −0.244	<.05
Epworth sleepiness score	−0.990	−0.256	−1.694 to −0.285	<.001
Beck depression score	−0.658	−0.517	−0.896 to −0.419	<.001
Constant term	−2.470			
$R^2 = 0.473$				

CI = confidence interval.

[*] Unstandardized coefficient.

[†] Standardized coefficient.

[‡] Factors from the initial simple linear regression analysis with $P \le .10$ included in the multivariate linear regression analysis: change in DAS28, pain, sleepiness, and depression scores.

[§] Factors from the initial simple linear regression with $P \le .10$ included in the multivariate regression analysis: change in DAS28, SJC, pain, sleepiness, and depression scores.

depression were retained in the multivariate model as factors explaining the variance in fatigue. The correlation of fatigue with disease activity is consistent with recent evidence.[40] However, the relationship of disease activity with fatigue in RA is unclear, and data available on this issue primarily come from cross-sectional studies,[41–44] while prospective evidence is scarce.[8]

The change in SJC was not identified as a contributor factor to fatigue in multivariate models performed in our series. These findings are in line with studies reporting that inflammatory components of the DAS28 contribute minimally to fatigue.[12] In addition, we found that other inflammatory parameters such as hemoglobin levels did not appear to be related to fatigue in line with previous reports.[6] Consistent with previous evidence, fatigue outcome appears to be independent of anemia.[40]

Regarding pain caused by joint inflammation, the bivariate analyses showed a significant correlation of pain with fatigue, although the multiple regression models did not identify pain as a factor explaining fatigue variance as seen with SJC. This finding is contrary to most cross-sectional studies conducted so far,[6,43,45] but consistent with a previous prospective study identifying predictors of fatigue over 1 year among RA patients.[8]

Taken together, these data suggest that fatigue variance after TCZ does not seem to be only explained by inflammatory activity, but physical and emotional functioning appear to have a greater contribution in our model as previously seen.[6,43] Accordingly, disease activity measured by DAS28 seemed to be contributing less strongly to fatigue variance than sleepiness and depression in the study multivariate models. At both study time points, sleepiness and depression explained variability in fatigue the best, depression being a stronger contributor. Our findings are therefore in line with previous studies that reported a significant association between fatigue variability and sleep quality or sleep disturbances.[6,46] However, it should be taken into account that the mean baseline sleepiness score is 6 and therefore RA patients evaluated in our series did not suffer from sleepiness because the Epworth scale considers a score between 0 and 9 as normal, and a mean reduction of about 1 point after 24 weeks is still within the normal range. In addition, duration of sleep was not found to be correlated with fatigue outcome. We cannot therefore clearly associate improvement in fatigue with changes in sleepiness score, despite its potential association.

Regarding cognitive and emotional functioning, depression was found to be strongly associated with fatigue, consistent with previous reports.[6,43] It is noteworthy that the mean baseline depression score in our series is nearly 18 and therefore patients had symptoms of moderate to severe depression. The baseline depressive mood of patients may be explained by their clinical activity at the time of TCZ treatment initiation, with high baseline disease activity (DAS28) and ESR scores, and a negative global perception of their disease (baseline VAS 6.6). Thus, the negative perception of disease may have contributed to fatigue through the mood state as these significantly fatigued RA patients (mean baseline FACIT <30) may perceive fatigue as frustrating or exhausting as previously seen.[6] The quality of life of patients with arthritis was previously investigated in several observational studies showing that all measures of disease activity and self-efficacy scores were markedly better in patients receiving biologic versus conventional therapy.[47] Therefore, improvement in depressive symptoms through the effect of TCZ on IL-6 levels may also improve fatigue. However, whether depression is the major cause of the improvement in fatigue in active RA cannot be clearly concluded as other psychosocial factors may be involved in RA fatigue besides depression.[8]

Finally, TCZ was reported to be well-tolerated with a withdrawal percentage due to adverse events <1%. The safety profile of TCZ presented no new or unexpected safety signals. The most common SAEs were infections as previously reported in clinical trials with TCZ.[26–28,48–50]

Some limitations of our study should be pointed out. Firstly, even though the change in sleepiness was identified as a contributor to fatigue improvement in the multivariate analyses, patients evaluated in our series did not suffer from sleepiness at that time point. Therefore, whether TCZ may reduce fatigue through the improvement of sleepiness would need to be addressed in RA patients with sleep disturbances. Secondly, our correlation analyses performed included relevant physical and psychosocial factors in addition to disease activity measures that have been involved in explaining fatigue in previous cross-sectional studies. However, we acknowledge that some inflammatory component such as CRP, ESR, and TJC, and other variables associated with RA fatigue such as disability and functioning, health-related quality of life, or self-efficacy were not

assessed in our model, or were not evaluated through a specific instrument. Other limitations to be highlighted are that RA is a heterogeneous disease and multiple comorbidities, and the requirement of drugs could affect some subjective complaints in different scores evaluated.

Despite its limitations, this study offers a welcome addition to the limited available prospective data on factors associated with RA fatigue, given that most evidence comes from cross-sectional studies. Additionally, the data existing on RA fatigue-related factors are heterogeneous mainly due to the use of different scales and questionnaires to evaluate fatigue and other PROs in addition to the assessment of different sets of variables in correlation studies. In this scenario, our study may provide the basis for a better understanding of factors explaining fatigue.

According to this, a recent paper on therapeutic strategies in patients affected by autoimmune rheumatic diseases will help in the near future to improve the unmet needs in the management of patients with RA.[51] Overall, we confirm this study supports and provides further evidence on the efficacy and safety of TCZ in clinical and psychological aspects in the real-world setting.

5. Conclusions

In summary, TCZ treatment results in a clinically significant improvement in fatigue that seems to correlate with disease activity reduction, although improvements in sleep and depressive symptoms appear to be stronger contributors to fatigue variance. Psychosocial factors therefore seem to have a more important role than inflammatory-related factors in explaining fatigue in active RA. Measuring the symptoms of fatigue in RA and individualization of therapeutic management based on mood state and depressive symptoms may therefore be of paramount importance in clinical practice, given that fatigue may be a reliable and feasible target to improve patient outcome.

Acknowledgments

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